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The Investigation and Treatment of Diabetic Gastroparesis

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ABSTRACT

Purpose: This review provides an update on the investigations and treatment options for gastroparesis.

Methods: A comprehensive literature search of Medline, PubMed, Embase and OVID was conducted which included all systematic reviews and research articles that focused on the diagnosis, investigations and management diabetic gastroparesis.

Findings: Dietary modifications and pharmacologic treatment with prokinetics to increase gastric motility form the mainstay of treatment. However, the use of prokinetics is limited by adverse effects and serious adverse effects, leaving metoclopramide as the only drug approved by the US Food and Drug Administration for the treatment of gastroparesis. Newer therapies, including motilin receptor agonists, ghrelin receptor agonists, and neurokinin receptor antagonists, are currently being investigated. Transpyloric stenting, gastric electrical stimulation, and gastric per-oral endoscopic myotomy provide mechanical options for intervention, and surgical interventions in severe intractable gastroparesis include laparoscopic pyloroplasty or gastrectomy.

Implications: Advances to better understand the pathophysiology and management of diabetic gastroparesis have been limited, especially with discordance between symptoms and severity of delay in gastric emptying. Established treatment options are limited; however, recent pharmacologic and surgical interventions show promise. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Gastroparesis, Microvascular.

INTRODUCTION

First described by Rundles in 1945,[1] the term *gastroparesis diabeticorum* was coined by Kassander in 1958.[2] The most common cause of gastroparesis, a condition characterized by delayed gastric emptying in the absence of a mechanical obstruction, is diabetes mellitus.[3,4] This condition can manifest in a variety of symptoms, including early satiety, nausea, vomiting, and anorexia. It can be associated with significant morbidity and impaired quality of life, with anxiety and depression and an effect on patients' self-management of diabetes, especially with fluctuating glucose levels.[5,6] However, the association between the severity of symptoms and delay in gastric emptying is not linear.[7] Indeed, up to 40% of patients with diabetic gastroparesis (DG) can be asymptomatic.[8] The term *gastric hypoglycemia* has been used to describe patients with hypoglycemia attributable to gastroparesis, and it should be considered in the differential diagnosis for patients diagnosed as having brittle diabetes.[9,10] A comprehensive literature

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EPIDEMIOLOGY

The exact prevalence of DG remains unknown. A major population-based study, evaluating symptoms, reported a 10-year cumulative incidence of gastroparesis of 5.2% in patients with type 1 diabetes mellitus (T1DM), 1.0% in patients with type 2 diabetes mellitus (T2DM), and 0.2% in controls.[11] The T1DM Exchange registry data reported 4.8% of patients had gastroparesis, with significant associations with female sex, longer duration of diabetes, older age, and more frequent severe hypoglycemic episodes, despite higher glycosylated hemoglobin (HbA_{1c}) levels.[12] Although less common than in patients with T1DM, the greater prevalence of T2DM means that more patients have gastroparesis attributable to this condition.[8] There are conflicting data on the prevalence of symptoms of gastroparesis in patients with diabetes.[13,14] In addition to delayed gastric emptying, patients may also develop rapid gastric emptying, with one study reporting this phenomenon in 22% of patients evaluated with scintigraphy.[15]

An interesting phenomenon is that of symptom turnover (the appearance and disappearance of symptoms over time), and several studies found this to be common in patients with DG. One study remarked that the turnover of symptoms was associated with depression rather than other factors, such as glycemic control.[16,17]

PATHOPHYSIOLOGY

The effective movement of gastric contents through the stomach depends on 2 major activities: peristalsis of gastric smooth muscle propelling contents to the pylorus and dilation of the pyloric sphincter. Interstitial cells of Cajal (ICCs) are specialized pacemaker cells that drive the contraction of gastric smooth muscle. The speed, strength, and, to a lesser degree, frequency of these contractions are known to be modified by both neurologic and neuroendocrine modulation.

Gastroparesis is defined as the delayed removal of stomach contents in the absence of a physical obstruction.[18] Hyperglycemia mediates nerve damage through a wide range of mechanisms, including poly–adenosine triphosphate ribose, advanced glycosylation end (AGE) products, endoplasmic reticulum stress, oxidative stress, inflammation, and ischemia,[19,20] which result in demyelination and axonal degeneration.[21,22] Neuropathy, affecting autonomic input, such as from the vagus nerve, or that affecting the enteric nervous system's own intrinsic neurons, can induce gastroparesis. Loss of parasympathetic stimulation will slow gastric emptying, a picture mimicked during surgical vagotomy.[23] Extensive myelinated and unmyelinated nerve fiber and endoneurial capillary pathologic findings have been found in the vagus nerve of diabetic patients with severe gastroparesis, although interestingly this was comparable to 2 diabetic patients without gastroparesis.[24] Both direct neurologic feedback from the small bowel and hormones, such as cholecystokinin and gastric inhibitory peptide, can limit the flow of chyme into the duodenum. Abnormalities of gastric electrical rhythm and transmission can lead to a disruption of the migrating motor complex, ineffective propulsion, and decreased pyloric output.[25,26] The severity of these arrhythmias has been directly linked to loss of ICCs, although not to the severity of symptoms.[27] The origin of gastroparesis has therefore been related to the pathologic features of the ICCs and vagal neurons.[28,29]

Neural nitric oxide synthase (nNOS) expressed in gastric neurons induces relaxation and accommodation, although its predominant function is to cause dilatation of gastrointestinal sphincters, including the pylorus.[29] In animal models of DG, reduced nNOS mRNA, protein, and function[30] restricts the passage of food into the duodenum. Interestingly, the reduction in nNOS is not attributable to a loss of active neurons but decreased expression on these intrinsic neurons.[8]

A significant decrease in ICC counts has been found in gastric biopsy specimens of patients with gastroparesis.[31–34] Interestingly, biopsy specimens of patients with gastroparesis-like syndrome (no evidence of delayed gastric emptying) reveal significantly lower ICC counts,[35] emphasizing their critical importance to gastroparesis. Indeed, a decreased ICC count is a key histologic finding in gastroparesis.[29] Unlike diabetic neuropathy where the deleterious effects stem from